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(54) Title: HEMOREGULATORY PEPTIDES

(57) Abstract

The invention provides compounds of the general formula (I): A^1-B^1-X^1-$(CH_2)_m$-$(CON(R_1))_r$-$(CH_2)_s$-Y^1-$(CH_2)_s$-$(N(R_1)CO)_r$-$(CH_2)_n$-X^1-B^1-A^1. The compounds of this invention are also illustrated by the formula (II): A^2-B^2-X^2-$(CH_2)_m$-$(CON(R_1))_r$-$(CH_2)_s$-Y^2-$(CH_2)_s$-$(N(R_1)CO)_r$-$(CH_2)_n$-X^2-B^2-A^2. The compounds of the invention have hemo-regulatory activity and can be used to stimulate haematopoiesis and can also be used for the treatment of certain symptoms caused by or arising out of viral, fungal and bacterial infectious diseases.

HEMOREGULATORY PEPTIDES

Field of the Invention

The present invention relates to novel compounds which have hemoregulatory activities and can be used to stimulate haematopoiesis and for the treatment of viral, fungal and bacterial infectious diseases.

Background of the Invention

A variety of regulatory messengers and modifiers such as colony stimulating factors, interferons, and different types of peptides are responsible for the regulation of myelopoiesis. Metcalf, Cell, 43:5 (1985); Baserga R., Foa P., Metcalf D, Polli EE (eds), Biological Regulation of Cell Proliferation (1986); Nicola et al., J. Cell Physiol. 128:501 (1986), Zoumbos et al., Proyr. Hemat. 1:341 and 14:201 (1986); Werner et al., Experientia 42:521 (1986).

In 1982, a synthetic hemoregulatory pentapeptide was reported to have a selective inhibitory effect on myelopoietic cells both in vitro and in vivo, where the main effect seems to be on myelopoietic stem cells (CFU-gm), Paukovits et al., Z. Naturforsch 37:1297 (1982) and U.S. Patent No. 4,499,081. This peptide is believed to be an analogue of a naturally occurring granulopoiesis inhibition factor which has been found in minute quantities in bone marrow extracts.

In 1987, Laerum et al., reported that the oxidation product of this peptide was a dimer (HP-5) formed by disulfide bridges. This dimer has the opposite effects of the monomer as it strongly stimulates colony formation of both human and murine CFU-gm in vitro and up-regulates murine myelopoietic cells in vivo. It is claimed in European Application No. 87309806.5

The dimer is reported as being useful in stimulating myelopoiesis in patients suffering from reduced myelopoietic activity, including bone marrow damage, agranulocytosis and aplastic anemia including patients having depressed bone marrow function due to immunosuppressive treatment to suppress tissue reactions i.e. in bone marrow transplant surgery. It may also be used to promote more rapid regeneration of bone marrow after cytostatic chemotherapy and radiation therapy for neoplastic and viral diseases. It may be of particular value where patients have serious infections due to a lack of immune response following bone marrow failure.

We have now found certain novel compounds which have a stimulative effect on myelopoietic cells and are useful in the treatment and prevention of viral, fungal and bacterial diseases.

Detailed Description of the Invention

The compounds of this invention are illustrated by the Formula (I):

$$A^1\text{-}B^1\text{-}X^1\text{-}(CH_2)_m\text{-}(CON(R_1))_r(CH_2)_s\text{-}Y^1\text{-}(CH_2)_s\text{-}(N(R_1)CO)_r(CH_2)_n\text{-}X^1\text{-}B^1\text{-}A^1 \quad (I)$$

wherein:

A^1 is independently proline, dehydroproline, pyroglutamic acid, glutamine, tyrosine, glutamic acid, 2-thiophene carboxylic acid, picolinic acid, nicotinic acid, isonicotinic acid, cyclohexane carboxylic acid, tetrahydrofuroic acid, oxothiazolidine carboxylic acid, cyclopentane carboxylic acid, thiophene carboxylic acid, tetrahydrofuran carboxylic acid, pipecolinic acid, piperidine carboxylic acid, pyrrole carboxylic acid, isopyrrole carboxylic acid, pyrazole carboxylic acid, isoimidazole carboxylic acid, triazole carboxylic acid, dithiole carboxylic acid, oxathiole carboxylic acid, isoxazole carboxylic acid, oxazole carboxylic acid,thiazole carboxylic acid, isothiazole carboxylic acid, oxadiazole carboxylic acid, oxatriazole carboxylic acid, oxathiolene carboxylic acid, oxazine carboxylic acid, oxathiazole carboxylic acid, dioxazole carboxylic acid, pyran carboxylic acid, pyrimidine carboxylic acid, pyridazine carboxylic acid, pyrazine carboxylic acid, piperazine carboxylic acid, triazine carboxylic acid, isooxazine carboxylic acid, oxathiazene carboxylic acid, morpholine carboxylic acid, indole carboxylic acid, indolenene carboxylic acid, 2-isobenzazole carboxylic acid, 1,5-pyridine carboxylic acid, pyranol[3,4-b]pyrrole carboxylic acid, isoindazole carboxylic acid, indoxazine carboxylic acid, benzoxazole carboxylic acid, anthranil carboxylic acid, quinoline carboxylic acid, isoquinoline carboxylic acid, cinnoline carboxylic acid, benzoic acid, quinazolene carboxylic acid, naphthyridine carboxylic acid, pyrido[3,4-b]-pyridine carboxylic acid, pyrido[3,2-b]-pyridine carboxylic acid, pyrido[4,3-b]pyridine carboxylic acid, 1,3,2-benzoxazine carboxylic acid, 1,4,2-benzoxazine carboxylic acid, 2,3,1-benzoxazine carboxylic acid, 3,1,4-benzoxazine carboxylic acid, 1,2-benzisoxazine carboxylic acid, 1,4-benzisoxazine carboxylic acid, carbazole carboxylic acid, acridine carboxylic acid, purine carboxylic acid, hydroxypicolinic acid, hydantoin carboxylic acid, furan carboxylic acid, N-acetyl proline, or azetidine carboxylic acid;

B^1 is independently serine, threonine, glutamic acid, tyrosine, aspartic acid, hydroxyproline, O-benzyl serine, N-methyl serine, N-methyl threonine, N-methyl glutamic acid, N-methyl tyrosine, N-methyl aspartic acid, 2-amino-3-

R_1, R_2 and R_3 are independently hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, C_{3-7} cycloalkyl, heteroaryl or aryl, all of which may be substituted by one or more C_{1-3} alkyl groups;

m and n are independently 0 to 5;

r is 0 to 2;

s is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In Formula II, A^2 and B^2 are connected via an amide bond, synthesized by condensing the amino group of A^2 and the carboxyl group of B^2.

"Aryl" means an aromatic ring or ring system of 5-10 carbon atoms, such as phenyl, benzyl, phenethyl, or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl.

"Heteroaryl" means an aromatic ring system containing one or more heteroatoms, such as imidazolyl, triazolyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, pyrrolyl, furanyl, or thienyl.

All alkyl, alkenyl, alkynyl and alkoxy groups may be straight or branched. The term "halogen" is used to mean iodo, fluoro, chloro or bromo. Alkyl groups may be substituted by one or more halogens up to perhalogenation.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and diastereoisomers are contemplated to be within the scope of the present invention.

Also included in this invention are pharmaceutically acceptable salt complexes of the compounds of this invention.

Preferred compounds of Formula I are those in which:

A^1 is pyroglutamic acid, picolinic acid, proline, pipecolinic acid, dehydroproline, azetidine carboxylic acid, or pyrole carboxylic acid;

B^1 is glutamic acid, serine, aspartic acid or N-methyl serine;

X^1 is NR_1;

m and n are 1 or 2;

Y^1 is phenyl or xylyl.

r is 1

s is 0

Especially preferred are:

N,N'-Bis(picolinyl-seryl-β-alanyl)-1,4-diaminobenzene;

N,N'-Bis(pyroglutamyl-glutamyl-β-alanyl)-1,4-diaminobenzene; and

N,N'-Bis(dehydroprolyl-seryl-β-alanyl)-1,4-diaminobenzene.

$$B^1—X^1—(CH_2)_m—CON(R_1)—(CH_2)_s—Y^1—(CH_2)_s—N(R_1)CO—(CH_2)_m—X^1—B^1 \quad (5)$$

Compound (5) is then reacted with A^1 wherein A^1 is as defined in Formula (I), using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N,N-dimethylformamide. Removal of the protecting groups with anhydrous hydrogen fluoride gives compounds of Formula (I).

b) Alternatively, a compound of Formula (I) wherein r is 1; s is 0 or 1; m and n are independently but not equivalently 0 to 5; X^1 is O, S or NR_1; and R_1 and Y^1 are as defined in Formula (I);
can be prepared by a process which comprises reacting a compound of Formula (6):

$$H(R_1)N—(CH_2)_s—Y^1—(CH_2)_s—N(R_1)P \quad (6)$$

wherein R_1 and Y^1 are as defined in Formula (I) and P is a suitable protecting group such as *t*-butyl carbamate, with a suitably protected carboxylic acid of Formula (3), using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N,N-dimethylformamide to provide a compound of Formula (7):

$$HX^1—(CH_2)_m—CON(R_1)—(CH_2)_s—Y^1—(CH_2)_s—N(R_1)P \quad (7)$$

Protecting group P is cleaved by a suitable reagent such as trifluoroacetic acid from compound (7) which is further reacted with a suitably protected carboxylic acid of Formula (8):

$$HX^1—(CH_2)_n—CO_2H \quad (8)$$

wherein X^1 is O, S or NR_1; and n is defined as in Formula (I), using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N,N-dimethylformamide to provide a compound of Formula (9):

$$HX^1—(CH_2)_m—CON(R_1)—(CH_2)_s—Y^1—(CH_2)_s—N(R_1)CO—(CH_2)_n—X^1H \quad (9)$$

wherein X^1 is CR_2R_3 s is 0 or 1 and m is 0 to 5; using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N,N-dimethylformamide to provide a compound of Formula (14):

$$Br—X^1—(CH_2)_m—CON(R_1)—(CH_2)_s—Y^1—(CH_2)_s—N(R_1)CO—(CH_2)_m—X^1—Br \quad (14)$$

The corresponding organomagnesium moiety of compound (14) is then reacted with the acid chloride of a suitably protected B^1 wherein B^1 is as defined in Formula (I), in the presence of a suitable catalyst such as copper (I) chloride, in a suitable solvent such as tetrahydrofuran to give a compound of Formula (15):

$$B^1—X^1—(CH_2)_m—CON(R_1)—(CH_2)_s—Y^1—(CH_2)_s—N(R_1)CO—(CH_2)_m—X^1—B^1 \quad (15)$$

Compound (15) is reacted with A^1 wherein A^1 is as defined in Formula (I), using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N,N-dimethylformamide. Removal of the protecting groups with anhydrous hydrogen fluoride gives compounds of Formula (I).

e) Alternatively, a compound of Formula (I) wherein r is 1; m and n are independently but not equivalently 0 to 5; X^1 is CR_2R_3; and R_1, R_2, R_3 and Y^1 are as defined in Formula (I); can be prepared by a process which comprises reacting a compound of Formula (6) with a suitably protected carboxylic acid of Formula (13), using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N,N-dimethylformamide to provide a compound of Formula (16):

$$Br—X^1—(CH_2)_m—CON(R_1)—(CH_2)_s—Y^1—(CH_2)_s—N(R_1)P \quad (16)$$

Protecting group P is cleaved by a suitable reagent such as trifluoroacetic acid from compound (16) which is further reacted with a suitably protected carboxylic acid of Formula (17):

$$Br—X^1—(CH_2)_n—CO_2H \quad (17)$$

The present invention provides compounds of Formula (II) which can be prepared by a process which comprises:

$$A^2-B^2-X^2-(CH_2)_m-(N(R_1)CO)_r-(CH_2)_s-Y^2-(CH_2)_s-(CON(R_1))_r-(CH_2)_n-X^2-B^2-A^2 \quad (II)$$

a) where r is 1; m and n are equivalently 0 to 5; s is as defined in Formula (II) and X is CO; reacting A^2 with a suitably protected B^2 wherein A^2 and B are defined as in Formula (I), using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N, N-dimethylformamide to provide a compound of Formula (22):

$$A^2—B^2 \quad (22)$$

Compound (22) is then reacted with a compound of Formula (23):

$$HO—X^2—(CH_2)_m—N(R_1)P \quad (23)$$

wherein X is CO; m is 0 to 4; P is a suitable protecting group such as t-butoxycarbonyl; and R_1 is as defined in Formula (II); using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N,N-dimethylformamide to give a compound of Formula (24):

$$A^2—B^2—X^2—(CH_2)_m—N(R_1)P \quad (24)$$

The protecting group P is cleaved by a suitable reagent such as trifluoroacetic acid from compound (24) and is further reacted with one half of an equivalent of a compound of Formula (25):

$$HO_2C—(CH_2)_s—Y^2—(CH_2)_s—CO_2H \quad (25)$$

wherein Y^2 is as defined in Formula (II); using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N,N-dimethylformamide. Removal of the protecting groups with anhydrous hydrogen fluoride gives compounds of Formula (II).

$$R_2—CO—(CH_2)_m—N(R_1)P \quad (30)$$

wherein P is a suitable protecting group such as t-butoxycarbonyl; under dehydration conditions. The resulting product is further reacted with a suitable reducing agent such as sodium cyanoborohydride to give a compound of Formula (31):

$$A^2—B^2—CHR_2—(CH_2)_m—N(R_1)P \quad (31)$$

The protecting group P is cleaved by a suitable reagent such as trifluoroacetic acid from compound (31) and is further reacted with one half of an equivalent of a compound of Formula (25) using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N,N-dimethylformamide. Removal of the protecting groups with anhydrous hydrogen fluoride gives compounds of Formula (II).

e) Alternatively, a compound of Formula (II) wherein r is 1; m and n are equivalently 0 to 5; X^2 is CR_2R_3; and s is defined in Formula (II); can be prepared by a process which comprises reacting a compound of Formula (22) with a compound of Formula (30) under dehydration conditions. The resulting product is further reacted with an organometallic species of Formula (32):

$$R_3—M \quad (32)$$

wherein M is a suitable metal such as lithium and R_3 is as defined in Formula (II); to give a compound of Formula (33):

$$A^2—B^2—CR_2R_3—(CH_2)_m—N(R_1)P \quad (33)$$

The protecting group P is cleaved by a suitable reagent such as trifluoroacetic acid from compound (33) and is further reacted with one half of an equivalent of a compound of Formula (25) using standard coupling reagents such as EDC/HOBt in a suitable solvent such as N,N-dimethylformamide. Removal of the protecting groups with anhydrous hydrogen fluoride gives compounds of Formula (II).

h) Alternatively, a compound of Formula (II) wherein r and s are 0; X^2 is CR_2R_3; R_3 is hydrogen and m and n are defined as in Formula (II); can be prepared by a process that comprises reacting a compound of Formula (22) with a compound of Formula (38):

$$R_2—CO—(CH_2)_m—Y^2—(CH_2)_n—CO—R_2 \qquad (38)$$

under dehydration conditions. The resulting product is further reacted with a suitable reducing agent such as sodium cyanoborohydride to give a compound of Formula (39):

$$A^2—B^2—CHR_2—(CH_2)_m—Y^2—(CH_2)_n—CHR_2—B^2—A^2 \qquad (39)$$

Removal of the protecting groups with an appropriate agent such as TFA, HF, HBr/HOAC or hydrogenation gives compounds of Formula (II).

i) Alternatively, a compound of Formula (II) wherein r and s are 0; X^2 is CR_2R_3 and m and n are defined as in Formula (II); can be prepared by a process that comprises reacting a compound of Formula (22) with a compound of Formula (38). The resulting product is further reacted with a organometallic species of Formula (32) to give a compound of Formula (40).

$$A^2—B^2—CR_2R_3—(CH_2)_m—Y^2—(CH_2)_n—CR_2R_3—B^2—A^2 \qquad (40)$$

Removal of the protecting groups with anhydrous hydrogen fluoride gives compounds of Formula (II).

In general, in order to exert a stimulatory effect, the peptides of the invention may be administered to human patients by injection in the dose range of 50 ng to 100 mg preferably 500 ng to 50 mg, or orally in the dose range of .05 mg to 50 mg, for example 100 µg to 10 mg per 70 kg body weight per day; if administered by infusion or similar techniques, the dose may be in the range 0.5 ng to 10 mg per 70 kg body weight, for example about 3 micrograms over six days. In principle, it is desirable to produce a concentration of the peptide of about
10^{-13}M to 10^{-2}M in the extracellular fluid of the patient.

gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

For rectal administration, a pulverized powder of the peptides of this invention may be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository. The pulverized powders may also be compounded with an oily preparation, gel, cream or emulsion, buffered or unbuffered, and administered through a transdermal patch.

Nasal sprays may be formulated similarly in aqueous solution and packed into spray containers either with an aerosol propellant or provided with means for manual compression.

Dosage units containing the compounds of this invention preferably contain .05-50 mg, for example .05-5 mg of the peptide of formula (I) or (II) or salt thereof.

According to a still further feature of the present invention there is provided a method of inhibition of myelopoiesis which comprises administering an effective amount of a pharmaceutical composition as hereinbefore defined to a subject.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) and (II) are demonstrated by the following tests.

Induction of Colony Stimulating Activity by Stromal Cells

The murine bone marrow stromal cell line, C6, is grown to confluency in plastic tissue culture dishes in RPMI-1640 medium and 5% FBS. On the day prior to the experiment this medium is changed to DMEM without added serum. To these cultures, the compounds are added in dose range of 0.1 picogram/ml to 100 microgram/ml for one hour, then washed from the cultures. The medium is replaced with fresh DMEM and the cells are incubated for 24 hours at 37°C, 5% CO_2. After 24 hours the C6 cell culture supernatant is collected, sterile filtered, and frozen until it can be assayed for the presence of hematopoietic colony stimulating activity (CSA) as set forth below.

Soft Agar Assay

Bone marrow cells are obtained from Lewis rats. They are adjusted to 10^6 cells/ml in DMEM without serum. A single layer agar system utilizing the following is used: DMEM enriched with nutrients ($NaHCO_3$, pyruvate, amino

CSF as a positive control, or excipient, daily. Seven days after irradiation and treatment begins, the mice are challenged with Candida albicans by intravenous administration. Note that this represents approximately a LD75 for normal mice. In other studies the mice are not immunosuppressed. In these studies the mice are treated starting seven days post infection in the same manner as the irradiated mice. In both models the mice are followed until moribund and the change is survival compared using the Wilcoxin test.

The examples which follow serve to illustrate this invention. The examples are intended to in no way limit the scope of this invention, but are provided to show how to make and use the compounds of this invention.

In the examples, all temperatures are in degrees Centigrade.

The abbreviations and symbols commonly used in the art are used herein to describe the peptides and reagents used in their synthesis.

Ala = alanine
Apy = 2-aminopyridine
Asp = aspartic acid
Cys = cysteine
DCU = dicyclohexylurea
DCC = dicyclohexylcarbodiimide
Glu = glutamic acid
HOB_t = 1 hydroxybenzyltriazole
$(Pr)_2NEt$ = diisopropylethylamine
NMM = N-methylmorpholine
PyBOP = benzotriazol-1-yloxy-tripyrrolidino phosphonium hexafluorophosphate
Ser = serine
tyr = tyrosine

CH_2Cl_2 (25 mL). $EtN(iPr)_2$ (4.00 mL, 22.9 mmol), picolinic acid (0.570 g, 4.63 mmol), HOBt (0.620 g, 4.59 mmol) and EDC (0.890 g, 4.64 mmol) were sequentially added. After 2 days at room temperature, the reaction mixture was poured into water (50 mL). The resulting precipitate was collected, washed with Et_2O (20 mL), water (50 mL) and dried under vacuum to give a yellow solid (1.17 g).

A portion of the crude material (0.18 g) was purified by flash chromatography (5 % to 10 % MeOH/EtOAc, silica gel) to give a white solid (0.03 g).

MS (ES+) m/z 815.4 (MH^+)

d) N,N'-Bis(picolinoyl-seryl-β-alanyl)-1,4-diaminobenzene

An HF vessel was charged with N,N'-bis(picolinoyl-seryl(Bzl)-β-alanyl)-1,4-diaminobenzene (68.9 mg, 85.0 mmol). Anhydrous HF(ca. 5 mL) was condensed into the vessel at -78 °C which was then sealed and warmed to 0 °C. After 1 h at 0 °C, the HF was removed *in vacuo*. The residue was then dissolved in 20 % MeOH/EtOAc and neutralized with solid $NaHCO_3$ (pH≈8). Removal of solvent gave a white residue which was subjected to flash chromatography (20 % MeOH/EtOAc, silica gel) to give 26.0 mg (48 %) of the title compound as a white solid.

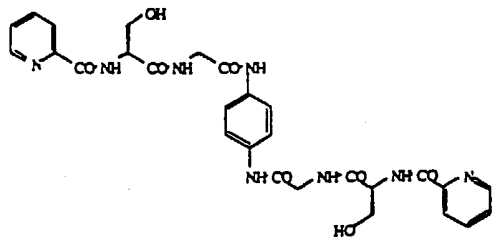
^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 2H), 8.67 (d, J = 7.5 Hz, 4H), 8.21 (m, 2H), 8.03 (m, 4H), 7.64 (m, 2H), 7.46 (s, 4H), 7.37 (s, 2H), 4.46 (m, 2H), 3.73 (dd, J = 13.9, 5.6 Hz, 2H), 3.66 (dd, J = 11.1, 5.6 Hz, 2H), 3.36 (m, 4H), 2.45 (m, 4H).

MS (ES+) m/z 635.2 (MH^+)

MS (ES-) m/z 633 (M - H)

EXAMPLE 2

N,N'-Bis(picolinoyl-seryl-glycyl)-1,4-diaminobenzene



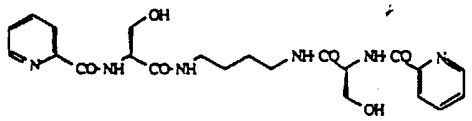
d) N,N'-Bis(picolinoyl-seryl-glycyl)-1,4-diaminobenzene

An HF vessel was charged with N,N'-bis(picolinoyl-seryl(Bzl)-glycyl)-1,4-diaminobenzene (41.2 mg, 52.0 µmol). Anhydrous HF (ca. 5 mL) was condensed into the vessel at -78 °C. The reaction vessel was then sealed and warmed to 0 °C. After 1 h, the HF was removed *in vacuo*, the residue dissolved in 20 % MeOH/EtOAc and made neutral with $NaHCO_3$ (pH=8). Removal of solvent gave a white solid which was subjected to flash chromatography (20 % MeOH/EtOAc, silica gel) to give 14 mg (44 %) of the title compound as a white solid.

^1H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 2H), 8.80 (d, J = 8.1 Hz, 2H), 8.68 (d, J = 5.4 Hz, 2H), 8.54 (m, 2H), 8.06 (m, 4 H), 7.65 (m, 2H), 7.55 (s, 4H), 5.31 (m, 2H), 4.55 (m, 2H), 3.91 (d, J = 5.4 Hz, 4H), 3.89 (m, 2H), 3.80 (m, 2H)
MS (ES+) m/z 607.2 (MH^+)
MS (ES-) m/z 605.2 (M - H)

EXAMPLE 3

N,N'-Bis(picolinoyl-seryl)-1,4-diaminobutane



a) N,N'-Bis(seryl(Bzl))-1,4-diaminobutane

To a solution of 1,4-diaminobutane (0.500 mL, 4.97 mmol) in CH_2Cl_2 (50 mL) was added BOC-Ser(Bzl) (3.23 g, 10.9 mmol), HOBt (1.48 g, 10.9 mmol), $EtNiPr_2$ (1.91 mL, 10.9 mmol) and EDC (2.10 g, 10.9 mmol). After 2 days at room temperature, the reaction was diluted with Et_2O (100 mL), washed with 1N HCl (20 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration gave a white foam (8.19 g).

A portion of the crude material (2.00 g) was subjected to flash chromatography (30 % EtOAc/hexane, silica gel) to give a white solid (0.39 g).
MS (ES+) m/z 643.0 (MH^+)
MS (ES-) m/z 687.2 ($M + HCOO^-$)

b) N,N'-Bis(picolinoyl-seryl(Bzl))-1,4-diaminobutane

To a solution of N,N'-bis(seryl(Bzl))-1,4-diaminobutane (0.23 g, 0.36 mmol) in CH_2Cl_2 (5 mL) was added TFA (1 mL). After 1 h at room

a) N,N'-Bis(BOC-seryl(Bzl))-1,4-diaminobenzene

To a suspension of 1,4-diaminobenzene dihydrochloride (0.500 g, 2.76 mmol) and BOC-Ser(Bzl) (1.79 g, 6.07 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added Et*N*iPr_2 (1.06 mL, 6.08 mmol). This was followed by DCC (1.25 g, 6.07 mmol) and DMAP (0.820 g, 6.71 mmol). After 22 h at room temperature, the reaction was diluted with Et_2O (50 mL) and filtered through a pad of celite. The celite was rinsed with additional Et_2O (100 mL). The combined organic portions were concentrated *in vacuo* to give an off-white solid (2.43 g). Flash chromatography (5 % MeOH/EtOAc, silica gel) gave 1.06 g (58 %) of the desired compound as a white solid.

MS (ES+) m/z 663.2 (MH^+)

b) N,N'-Bis(picolinoyl-seryl(Bzl))-1,4-diaminobenzene

To a solution of N,N'-bis(BOC-seryl(Bzl))-1,4-diaminobenzene (0.47 g, 0.71 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL). After 1.5 h at room temperature, the solvent was removed *in vacuo*. The residue was redissolved in CH_2Cl_2 (10 mL) and Et*N*iPr_2 (0.54 mL, 2.1 mmol), picolinic acid (0.19 g, 1.5 mmol), HOBt (0.21 g, 1.5 mmol) and DCC (0.32 g, 1.5 mmol) were added sequentially. After 18 h, the reaction was diluted with Et_2O (50 mL) and filtered through a pad of celite. The celite was further rinsed with Et_2O (50 mL) and the combined organic portions were concentrated to give an orange oil (1.54 g). Flash chromatography (10 % MeOH/EtOAc, silica gel) gave 0.51 g (quantitative) of the desired compound as a white solid.

MS (ES+) m/z 673.2 (MH^+)

MS (ES-) m/z 671.2 (m - H)

c) N,N'-Bis(picolinoyl-seryl)-1,4-diaminobenzene

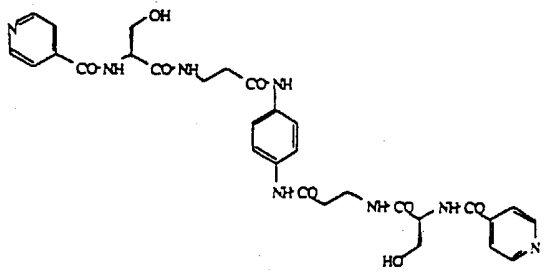
An HF vessel was charged with N,N'-bis(picolinoyl-seryl(Bzl))-1,4-diaminobenzene (0.108 g 0.161 mmol). Anhydrous HF (ca. 5 mL) was condensed into the vessel at -78 °C. The reaction vessel was sealed and warmed to 0 °C. After 1 h, the HF was removed *in vacuo*, the residue dissolved in 20 % MeOH/EtOAc and neutralized with $NaHCO_3$. This was concentrated to give a white solid (0.229 g).

A portion of the crude material (0.15 g) was subjected to flash chromatography (5 % MeOH/EtOAc, silica gel) to give 14.0 mg of pure product as a white solid.

sealed and warmed to 0 °C. After 1 h, the HF was removed *in vacuo*. The residue was partitioned between Et_2O (75 mL) and H_2O (25 mL). The organic phase was extracted with H_2O (25 mL) and 0.1N AcOH (25 mL). The combined aqueous extracts were concentrated *in vacuo* to ca. 1/3 its original volume. The remaining solution was lyophilized to yield a white powder (25.8 mg). Reverse phase preparative HPLC (5 % to 20 % CH_3CN/H_2O (0.1 % TFA), Hamilton PRP-1 HPLC prep column) gave the title compound (21.1 mg).
MS (ES+) m/z 635.2 (MH^+)

EXAMPLE 6

N,N'-Bis(isonicotinoyl-seryl–β–alanyl)-1,4-diaminobenzene



a) N,N'-Bis(isonicotinoyl-seryl(Bzl)–β–alanyl)-1,4-diaminobenzene

To a solution of N,N'-bis(BOC-seryl(Bzl)–β–alanyl)-1,4-diaminobenzene (0.38 g) as prepared in Example 1, in CH_2Cl_2 (15 mL) was added TFA (15 mL). After stirring for 1 hr at room temperature, the mixture was concentrated *in vacuo*. The residue was azeotroped with toluene (ca. 2 mL). The resulting oil was taken up in DMF(2 mL) and EtNiPr2 (0.65 mL, 3.7 mmol) was added. A portion (1.3 mL) of this solution was added to a solution of isonicotinoyl chloride hydrochloride (0.12 g, 0.66 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The reaction was warmed to room temperature. After 18 h, the reaction was quenched by pouring into a mixture of 5% Na_2CO_3 in brine (100 mL) and Et_2O (50 mL). The resulting precipitate was collected, washed with Et_2O and dried under vacuum to yield a white powder (0.20 g).

A portion of the crude material was purified by flash chromatography (20% MeOH/EtOAc, silica gel) to give a white powder (33 mg).
MS (ES+) m/z 815.2 (MH^+)

b) N,N'-Bis(pyroglutamoyl-glutamoyl(OBzl)–β–alanyl)-1,4-diaminobenzene

To a solution of N,N'-bis(BOC-glutamoyl(OBzl)–β–alanyl)-1,4-diaminobenzene (0.48 g, 0.54 mmol) in CH_2Cl_2 (6 mL) was added TFA (3 mL). The reaction was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in DMF (5 mL). $EtNiPr_2$ (0.94 mL, 5.4 mmol), p-Glu (0.21 g, 1.6 mmol), HOBt (0.44 g, 3.3 mmol) and BOP reagent (0.72 g, 1.6 mmol) were sequentially added. After 48 h, the reaction was poured into a mixture of 1N HCl (50 mL), brine (50 mL) and Et_2O (50 mL). The resulting precipitate was collected and dried under vacuum to give a white solid (0.80 g)

A portion (0.28 g) of the crude material was resuspended in EtOAc (50 mL) and 1N HCl (50 mL). The precipitate was collected, washed with EtOAc (20 mL), water (20 mL) and dried under vacuum to give the desired compound as a white solid (0.11 g).
MS (ES+) m/z 889.4 (MH^+)

c) N,N'-Bis(pyroglutamoyl-glutamoyl–β–alanyl)-1,4-diaminobenzene

An HF vessel was charged with N,N'-bis(pyroglutamoyl-glutamoyl(OBzl)-β-alanyl)-1,4-diaminobenzene (30 mg 0.03 mmol). Anhydrous HF (ca. 5 mL) was condensed into the vessel at -78 °C. The reaction vessel was sealed and warmed to 0 °C. After 1 h, the HF was removed *in vacuo*, the residue was partitioned between 1 % TFA/H_2O (20 mL) and Et_2O (10 mL). The Et_2O layer was discarded and the aqueous phase was lyophilized to give the title compound (27 mg).
^1H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 2H), 8.11 (d, J = 8.0 Hz, 2H), 8.01 (broad s, 2H), 7.79 (s, 2H), 7.49 (s, 4H), 4.23 (m, 2H), 4.06 (m, 2H), 3.30 (m, 4H), 2.50 (m, 8H), 2.30 - 1.70 (m, 8H)
MS (ES+) m/z 731.2 (MH^+)
MS (ES-) m/z 729.0 (M - H)

c) N-5'-(Pyroglutamoyl-glutamoyl(OBzl)-amino)pentyl-6-(pyroglutamoyl-glutamoyl(OBzl)-amino)hexanamide

To a solution of N-5'-(BOC-glutamoyl(OBzl)-amino)pentyl-6-(BOC-glutamoyl(OBzl)-amino)hexanamide (1.93 g, 1.04 mmol) in CH_2Cl_2 (14 mL) was added TFA (6 mL). The reaction was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in DMF (10 mL). Et*i*Pr$_2$ (2.70 mL, 15.5 mmol), p-Glu (0.45 g, 3.10 mmol), HOBt (0.42 g, 3.11 mmol) and BOP reagent (1.37 g, 3.10 mmol) were sequentially added. After 48 h, the reaction was poured into a mixture of water (50 mL) and EtOAc. The resulting precipitate was collected, rinsed with Et_2O and dried under vacuum to give the desired compound as a white solid.

MS (ES+) m/z 876.2 (MH^+)

MS (ES-) m/z 920 (m + HCO_2^-)

d) N-5'-(Pyroglutamoyl-glutamoyl-amino)pentyl-6-(pyroglutamoyl-glutamoyl-amino)hexanamide

An HF vessel was charged with N-5'-(pyroglutamoyl-glutamoyl(OBzl)-amino)pentyl-6-(pyroglutamoyl-glutamoyl(OBzl)-amino)hexanamide (92 mg 0.11 mmol). Anhydrous HF (ca. 5 mL) was condensed into the vessel at -78 °C. The reaction vessel was sealed and warmed to 0 °C. After 1 h, the HF was removed *in vacuo*, the residue was partitioned between 1 % TFA/H_2O (20 mL) and Et_2O (10 mL). The Et_2O layer was discarded and the aqueous phase was lyophilized to give the title compound (46 mg)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 7.9 Hz, 2H), 7.91 (m, 2H), 7.91 (s, 2H), 7.73 (m, 2H), 4.90 (broad s, 1H), 4.23 (m, 2H), 4.07 (m, 2H), 3.00 (m, 6H), 2.30 -2.00 (m, 12H), 1.90 (m, 4H), 1.75 (m, 2H), 1.50 - 1.38 (m, 8H), 1.24 (m, 4H)

MS (ES+) m/z 696.2 (MH^+)

MS (ES-) m/z 694.2 (M - H)

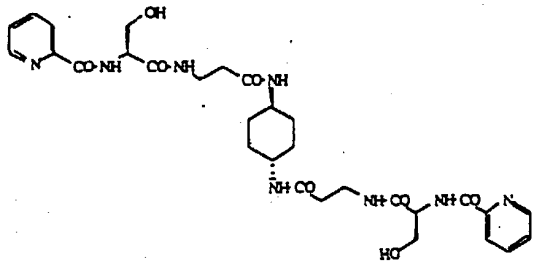
removed *in vacuo* and the residue was dissolved in DMF (5 mL). $EtNiPr_2$ (0.14 mL, 0.80 mmol), picolinic acid (0.03 g, 0.24 mmol), HOBt (0.07 g, 0.52 mmol) and BOP reagent (0.11 g, 0.25 mmol) were sequentially added. After 24 h, the reaction was poured into water (50 mL). The resulting precipitate was collected, rinsed with H_2O and dried under vacuum to give the desired compound (0.08 g).
MS (ES+) m/z 865.4 (MH^+)
MS (ES-) m/z 863.2 (M - H)

d) N,N'-Bis(picolinoyl-seryl-β-alanyl)-1,5-diaminonapthalene

An HF vessel was charged with N,N'-bis(picolinoyl-seryl(Bzl)-β-alanyl)-1,5-diaminonapthalene (14 mg 0.02 mmol). Anhydrous HF (ca. 5 mL) was condensed into the vessel at -78 °C. The reaction vessel was sealed and warmed to 0 °C. After 1 h, the HF was removed *in vacuo*, the residue was partitioned between 1 % TFA/H_2O (20 mL) and Et_2O (10 mL). The Et_2O layer was discarded and the aqueous phase was lyophilized to give the title compound.
^1H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 2H), 8.70 (m, 4H), 8.25 (m, 2H), 8.05 (m, 4H), 7.90 (m, 2H), 7.65 (m, 4H), 7.50 (m, 2H), 4.50 (m, 2H), 3.70 (m, 4H), 3.35 (m, 4H), 2.70 (m, 4H)
MS (ES+) m/z 685.2 (MH^+)
MS (ES-) m/z 797.2 (M^- + TFA)

EXAMPLE 10

trans-N,N'-Bis(picolinoyl-seryl-β-alanyl)-1,4-diaminocyclohexane



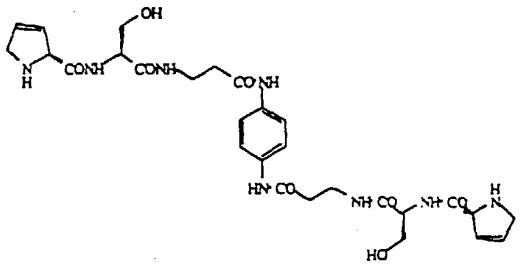
a) *trans*-N,N'-Bis(BOC-β-alanyl)-1,4-diaminocyclohexane

To a solution of *trans*-1,4-diaminocyclohexane (0.50 g, 4.38 mmol) in DMF (25 mL) was added BOC-β-Ala (2.48 g, 13.1 mmol), HOBt (3.55 g, 26.3 mmol), BOP reagent (5.81 g, 13.1 mmol) and $EtNiPr_2$ (7.60 mL, 43.6 mmol). After 20 h at room temperature, the reaction was poured into a mixture

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (m, 4H), 8.36 (m, 2H), 8.05 (m, 6H), 7.60 (m, 2H), 5.41 (m, 1H), 5.08 (m, 1H), 4.41 (m, 1H), 3.70 (m, 5H), 3.45 (m, 2H), 3.27 (m, 4H), 2.21 (m, 4H), 1.74 (m, 4H), 1.17 (m, 4H)
MS (ES+) m/z 641.2 (MH^+)

EXAMPLE 11

N,N'-Bis(3,4-dehydroprolyl-seryl-β-alanyl)-1,4-diaminobenzene



a) N,N'-Bis(3,4-dehydroprolyl-seryl(Bzl)-β-alanyl)-1,4-diaminobenzene

In a manner similar to Example 1(c), N,N'-bis(BOC-seryl(Bzl)-β-alanyl)-1,4-diaminobenzene (0.38 g, 0.35 mmol) was reacted with TFA (10 mL) in CH_2Cl_2 (10 mL). After 1 h, the solvent was removed *in vacuo* and the residue dissolved in DMF (2 mL). A portion of this solution (1 mL)was removed and reacted in a manner similar to Example 1(c) with EtN^iPr_2 (0.10 mL, 0.57 mmol), BOC-3,4-dehydroproline (0.11 g, 0.53 mmol), HOBt (0.12 g, 0.86 mmol) and BOP reagent (0.24 g, 0.53 mmol) to give a white precipitate. Flash chromatography (10 % MeOH/EtOAc, silica gel) gave pure product (73 mg).
MS (ES+) m/z 995.4 (MH^+)

b) N,N'-Bis(3,4-dehydroprolyl-seryl-β-alanyl)-1,4-diaminobenzene

In a manner similar to Example 1(d), N,N'-bis(3,4-dehydroprolyl-seryl(Bzl)-β-alanyl)-1,4-diaminobenzene (41.1 mg, 0.041 μmol) was reacted with anhydrous HF (ca. 5 mL) to give crude product (28.1 mg). Preparative reverse phase HPLC (5 % to 80 % CH_3CN/H_2O and 0.1 % TFA, Hamilton PRP-1 column) gave 15.1 mg (59 %) of the title compound as a white solid.
MS (ES+) m/z 615.2 (MH^+)

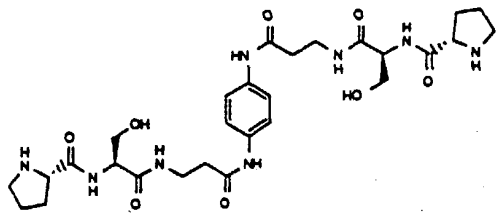
b) N, N'-Bis(2-pyrrole carbonyl-seryl-β-alanyl)-1,4-diaminobenzene

N, N'-Bis(2-pyrrole carbonyl-seryl(Nzl)-β-alanyl)-1,4-diaminobenzene (14 mg, 17 μmol) was dissolved in p-cresol (0.5 mL) in a 50-mL Teflon HF cleavage vessel fitted with a magnetic stirring bar. The vessel was cooled to -78 °C and evacuated using a water aspirator. Anhydrous HF (ca. 5 mL) was condensed into the vessel, the cooling bath was changed to 0 °C, and the reaction was stirred for 1 h. The HF was carefully removed under aspirator vacuum, the residue was taken up in Et_2O (25 mL), then extracted with H_2O (4 x 25 mL) and 0.1 N HOAc (1 x 25 mL). The combined aqueous layers were concentrated *in vacuo* to less than one-third volume, frozen and lyophilized to a white powder. Purification by reverse-phase HPLC (CH_3CN/H_2O+ 0.1% TFA, gradient, Hamilton PRP-1) gave 7 mg (66 %) of the title compound.

MS (ES+) m/z 611.2 (MH^+).

EXAMPLE 13

N, N'-Bis(prolyl-seryl-β-alanyl)-1,4-diaminobenzene



a) N, N'-Bis(BOC-prolyl-seryl(Bzl)-β-alanyl)-1,4-diaminobenzene

N, N'-Bis(BOC-seryl(Bzl)-β-alanyl)-1,4-diaminobenzene (101 mg, 126 μmol) prepared as in Example 1, was suspended in CH_2Cl_2 (2 mL) and neat TFA (2 mL) was added, causing the mixture to become homogeneous immediately. After stirring for 90 min at room temperature, the mixture was

a) N-BOC-azetidine carboxylic acid

To a suspension of azetidine-2-carboxylic acid (1.04 g, 10.3 mmol) in dioxane (25 mL) was added 5% $NaHCO_3$ (25 mL) and n-butanol (3 mL). Di-t-butyl dicarbonate (2.23 g, 10.2 mmol) was added and the reaction was stirred for 24 h at room temperature. The reaction was quenched by adding H_2O (50 mL) and $CHCl_3$ (100mL). The mixture was acidified to pH 2 by the careful addition of 3N H_2SO_4. After separating the phases, the aqueous layer was extracted further with $CHCl_3$ (2 x 50mL). The combined organic layers were washed with 1N HCl (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a clear oil. Recrystallization from EtOAc/hexane yielded 1.56 g of the desired compound. The mother liquor was concentrated *n vacuo* to give another 406 mg of the desired product (95 %).

MS (ES+) m/z 202.0 (MH^+).

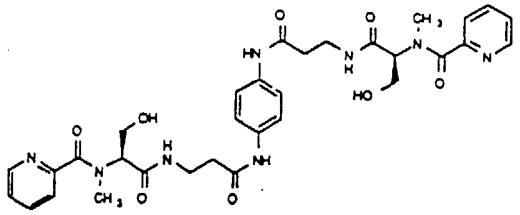
b) N, N'-Bis(BOC-azetidine carbonyl-seryl-β-alanyl)-1,4-diaminobenzene

In an analogous fashion to Example 13 (a), deprotection of N, N' bis(BOC-seryl(Bzl)-β-alanyl)-1,4-diaminobenzene (102 mg, 126 μmol) in CH_2Cl_2 (1 mL) and TFA (1 mL) followed by reaction with DIEA (220 μL, 1.3 mmol), HOBt (86 mg, 637 μmol), N-BOC-azetidine carboxylic acid (76 mg, 378 μmol), and BOP reagent (281 mg, 636 μmol) in DMF (1 mL) gave 43 mg (36 %) of the desired compound as a white powder after flash chromatography (15 % MeOH/EtOAc, silica gel).

MS (ES+) m/z 971.4 (MH^+).

EXAMPLE 15

N, N'-Bis (picolinoyl-N-methyl-seryl-β-alanyl)-1,4-diaminobenzene

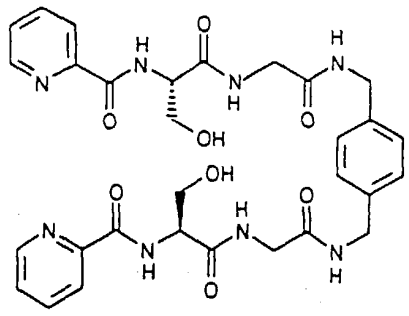


a) N, N'-Bis(Fmoc-N-methyl-seryl-β-alanyl)-1,4-diaminobenzene

N,N' Bis(BOC-β-alanyl)-1,4-diaminobenzene (90 mg, 199 μmol) prepared as in Example 1was suspended in CH_2Cl_2 (1 mL) and neat TFA (1 mL) was added, causing the mixture to become homogeneous immediately. After stirring for 90 min at room temperature, the mixture was concentrated *in vacuo* to an orange oil, which was taken up in DMF (1 mL) and neutralized with DIEA (420 μL, 2.4 mmol).

Fmoc-N-MeSer(Bzl) (259 mg, 601 μmol) was dissolved in DMF (5mL). HOBt (135 mg, 997 μmol) and BOP reagent (267 mg, 604 μmol) were added and the mixture was stirred for 5 min. The activated amino acid was then added to the product obtained above and the reaction was stirred for 18 h. The reaction was added to a rapidly-stirred mixture of Et_2O (50 mL) and 5% Na_2CO_3 in brine (100 mL), resulting in formation of a white precipitate. This was collected and dried under vacuum to obtain 259 mg of the desired product as a white powder. This was used in the next step without further purification.
MS (ES+) m/z 1077.4 (MH^+).

EXAMPLE 16



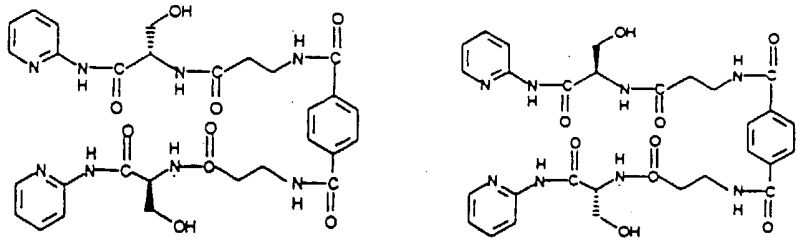
Preparation of (Pic-Ser-Gly)$_2$-α,α'-diamino-p-xylene

a) *(Boc-Gly)*$_2$-PDAX: Boc-Gly-OH (876 mg, 5 mmol) was dissolved in CH_2Cl_2 (25 mL), HOBt (676 mg, 5mmol) and DCC (1032 mg, 5 mmol) were added and the mixture was stirred for 15 min. Precipitated DCU was filtered off and washed with CH_2Cl_2 (5 mL). The combined filtrate and washing were added to a prepared solution of α,α'-diamino-p-xylene (PDAX; 341 mg, 2.5 mmol) and Pr^i_2NEt (0.92 mL, 5 mmol) in CH_2Cl_2 (25 mL). A precipitate was formed immediately. The mixture was stirred overnight and was then rotary evaporated and dried under high vacuum. The residue was triturated with 5% aq $NaHCO_3$ (50 mL) and the product extracted into CH_2Cl_2 (total 150 mL; some MeOH was added to aid dissolution). The combined extracts were dried on $MgSO_4$, filtered and evaporated to dryness. The residue was reprecipitated from Et_2O and filtered. After drying, the title compound (958 mg, 85.1%) was obtained as a very white soft powder. TLC R_f 0.44 (85:10:5 $CHCl_3$/MeOH/AcOH).

b) *(Z-Ser(t-Bu)-Gly)*$_2$-PDAX: (Boc-Gly)$_2$-PDAX (400 mg, 0.89 mmol) was dissolved in 1% H_2OCF_3COOH (40 mL) and the solution stirred for 90 min. It was then rotary evaporated, coevaporated twice with PhMe (10mL each) and dried under high vacuum. The oily residue of (H-Gly)$_2$-PDAX.2CF_3COOH was redissolved in DMF (15 mL) and added to Z-Ser(*t-Bu*)-OH (680 mg, 1.77 mmol), preactivated with PyBOP (923 mg, 1.77 mmol), HOBt (240 mg, 1.77 mmol) and NMM (0.49 mL, 4.43 mmol) in DMF (5 mL). The mixture was stirred overnight, evaporated under waterpump vacuum at 60°, treated with 5% aq $NaHCO_3$ (50 mL) and extracted into CH_2Cl_2 (3 x 25 mL). The combined extracts were washed with 10% aq citric acid and 2 M aq NaCl (25 mL each), dried on $MgSO_4$, filtered, evaporated and taken to dryness under high vacuum. The title compound was obtained as a colorless oil. TLC R_f0.57 (85:10:5 $CHCl_3$/MeOH/AcOH).

EXAMPLES 17 and 18

(Apy-L-Ser-βAla)$_2$-terephthalate and (Apy-D-Ser-βAla)$_2$-terephthalate



(The synthesis of the above compounds were carried out in parallel)

Preparation of (Apy-L-Ser-βAla)$_2$-terephthalate and (Apy-D-Ser-βAla)$_2$-terephthalate

a) *Z-Ser(t-Bu)-Apy:* Z-L-Ser(t-Bu)-OH or Z-D-Ser(t-Bu)-OH (1.92 g, 5 mmol) was dissolved in CH_2Cl_2 (25 mL). HOBt (0.68 g, 5 mmol) and DCC (1.03 g, 5 mmol) were added. The mixture was stirred for 15 min, then the DCU was filtered off. The filtrate was added to a solution of 2-aminopyridine (Apy; 0.47g, 5mmol) and i-Pr_2NEt (0.87 mL, 5 mmol) in CH_2Cl_2 (25 mL) and the entire mixture was stirred overnight. It was then diluted to 100 mL with additional CH_2Cl_2 and extracted with 5% aq $NaHCO_3$ (2 x 25 mL) and 2 M aq NaCl (25 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (3 cm diam. column; 7.5% Et_2O/CH_2Cl_2) to yield 444 mg (23.9%) or 373 mg (26.1%) of glassy solid L- or D-product, respectively. TLC R_f 0.70 (85:10:5 $CHCl_3$/MeOH/AcOH).

b) *Z-βAla-(L and D) Ser(t-Bu)-Apy* ; Z-Ser(t-Bu)-Apy (444 mg, 1.2 mmol) was dissolved in MeOH (50 mL) and hydrogenated using 10% Pd/C (120 mg). After a reaction period of 1 h, the catalyst was filtered off and the filtrate evaporated to dryness. The intermediate H-Ser(t-Bu)-Apy (TLC:R_f 0.15; 85:10:5 $CHCl_3$/MeOH/AcOH; UV & ninhydrin) was redissolved in DMF (25 mL) and added to a prepared solution of Z-βAla-OH (268 mg, 1.2 mmol), PyBOP (624 mg, 1.2 mmol), HOBt (162 mg, 1.2 mmol) and NMM (0.26 mL, 1.8 mmol) in DMF (5 mL). The mixture was stirred overnight, evaporated, triturated with 5% aq $NaHCO_3$ (50 mL) and extracted into CH_2Cl_2 (3 x 30 mL). The extract was washed with 2 M aq NaCl (25 mL), dried over $MgSO_4$, filtered and evaporated. The title compound was obtained as a colourless oil (TLC R_f 0.56, 85:10:5 $CHCl_3$/MeOH/AcOH).

EXAMPLE 19

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Tablets/Ingredients		Per Tablet
1.	Active ingredient (Cpd of Form. I or II)	0.5 mg
2.	Corn Starch	20 mg
3.	Alginic acid	20 mg
4.	Sodium alginate	20 mg
5.	Mg stearate	1.3 mg

Procedure for tablets:

Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its converion to wet granules.

Step 3 The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4 The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5 The dry granules are lubricated with ingredient No. 5.

Step 6 The lubricated granules are compressed on a suitable tablet press.

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I or II in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

hydroxythiopropanoic acid, 2-amino-1-hydroxypropyl or 2-amino-1-hydroxypent-3-enyl;

X^1 is O, S, NR_1 or CR_2R_3;

Y^1 is heteroaryl, O, S, NR_1, CR_2R_3, aryl, C_{2-5}alkyl, C_{2-5} alkenyl, or C_{2-5} alkynyl, napthyl, xylyl, $CON(R_3)$, piperazine, biphenyl, diacetylene benzene or divinyl benzene;

R_1, R_2 and R_3 are independently hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, C_{3-7} cycloalkyl, heteroaryl or aryl, all of which may be substituted by one or more C_{1-3} alkyl groups;

m and n are independently 0 to 5;

r is 0 to 2; and

s is 0 or 1;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 wherein A^1 is pyroglutamic acid, picolinic acid, proline, pipecolenic acid, dehydroproline, azetidine carboxylic acid or pyrole carboxylic acid; B^1 is glutamic acid, serine, aspartic acid or N-methyl serine; X^1 is NR_1; m and n are 1 or 2 and Y^1 is phenyl or xylyl; r is 1 and s is 0.

3. A compound of formula II:

$$A^2\text{–}B^2\text{–}X^2\text{–}(CH_2)_m\text{–}(N(R_1)CO)_r\text{–}(CH_2)_s\text{–}Y^2\text{–}(CH_2)_s\text{–}(CON(R_1))_r\text{–}(CH_2)_n\text{–}X^2\text{–}B^2\text{–}A^2 \quad \text{(II)}$$

wherein:

A^2 is independently 3-aminopyrazole, 5-aminopyrazole, aminothiazole, aminopyrimidine, aminothiadiazole, aminopyridazine, 2-aminopyridine, 3-aminopyridine, 4-aminopyridine, aminopurine, aminopteridine, 3-aminoisoxazole, 5-aminoisoxazole, 3-amino-1,2,4-triazine, 2-amino-1,3, 5-triazine, aminodimethyluracil, aminomethyluracil, 2-amino-3-hydroxypyridine, 2-amino-4-hydroxpyridine, 3-(aminomethyl)pyridine, 4-(aminomethyl)pyridine, aniline, 3-aminopyrrolidine, aminoquinoline, aminotetrazole, 3-amino-1,2,4-triazole, 5-aminouracil, 6-aminouracil, aminopyrrole, aminofuran, aminothiophene, 3-aminopiperidine, 4-aminopiperidine, cyclohexylamine, cyclopentylamine, pyrazolo [3,4-b]pyridine, 3-aminobutyrolactam or 2-aminocyclopentinone.

B^2 is independently serine, threonine, glutamic acid, tyrosine, aspartic acid, hydroxyproline, O-benzyl serine, N-methyl serine, N-methyl threonine, N-methyl glutamic acid, N-methyl tyrosine, or N-methyl aspartic acid,

X^2 is CO or CR_2R_3;

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/05859

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 37/00, 37/02; C07C 5/02

US CL : 514/18, 19; 530/323, 332

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/18, 19; 530/323, 332

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE (GENERIC STRUCTURE)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 4,732,970 (FIELDS ET AL.) 22 March 1988, columns 1-2.	1-9
A	US,A, 4,310,517 (ETSCHENBERG ET AL.) 12 January 1982, columns 1-2.	1-9
A	US,A, 4,859,654 (HOOVER ET AL.) 22 August 1989, column 2, lines 13-63.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 09 AUGUST 1994	Date of mailing of the international search report SEP 08 1994
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